1-11-2020

Update on Oral Oncolytics

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Disclosures

The author of this presentation has no relevant financial or non-financial relationships in the products described and reviewed in this presentation.

Objectives

- Review the history and development of oral oncolytics
- Compare and contrast the differences between oral and parenteral chemotherapy
- Understand the most common misconceptions of oral oncolytics
- Review the pharmacy practice standard for oral oncolytic therapy developed by the Hematology/Oncology Pharmacy Association (HOPA)
- Highlight some of the recently approved oral oncolytics and review their indication, adverse effects, and place in therapy

Definitions

Chemotherapy

- Treatment to stop the growth of cancer cells either by killing them or stopping them from dividing

Oncolytic

- To cause oncolysis, or a destruction of tumor cells but not normal cells

Targeted therapy

- A substance that attacks specific types of cancer cells with less harm to normal cells

Cytotoxic

- A substance that kills cells, including cancer cells

Cytostatic

- A substance that slows or stops the growth of cells, including cancer cells, without killing them

NCI Dictionary of Cancer Terms

Introduction

- Oral oncolytics are a broad pharmacologic class made up of oral cytotoxic agents and small-molecule inhibitors (i.e. targeted therapy)
- Standard chemotherapy is generally cytotoxic while newer, targeted therapies are often cytostatic

J Natl Compr Canc Netw 2008;6(3):S1-15.; Image Courtesy of Labroots.com

Question 1

True or False

- Oral chemotherapy agents were developed within the last 20 years.

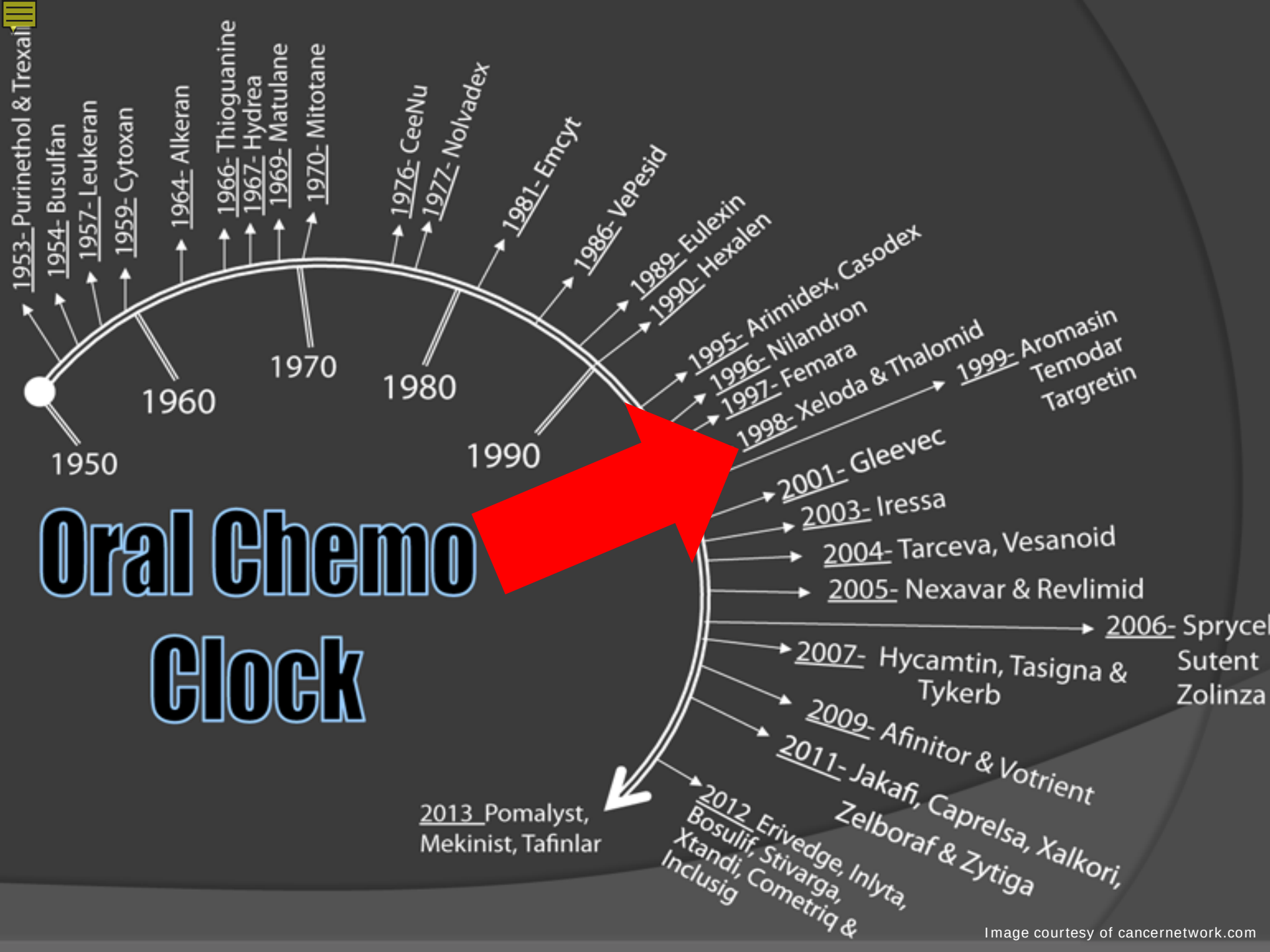


Image courtesy of cancernetwork.com

Drug Delivery

Parenteral	Oral
Consistent absorption	Variable absorption
Maximally tolerated single dose	Low daily maintenance dose
Tumor cells killed during single administration	Tumor cells continuously exposed
Requires bone marrow recovery period	Does not require bone marrow recovery period
Limited number of cycles	Indefinite treatment length

J Natl Compr Canc Netw 2008;6(3):S1-15.

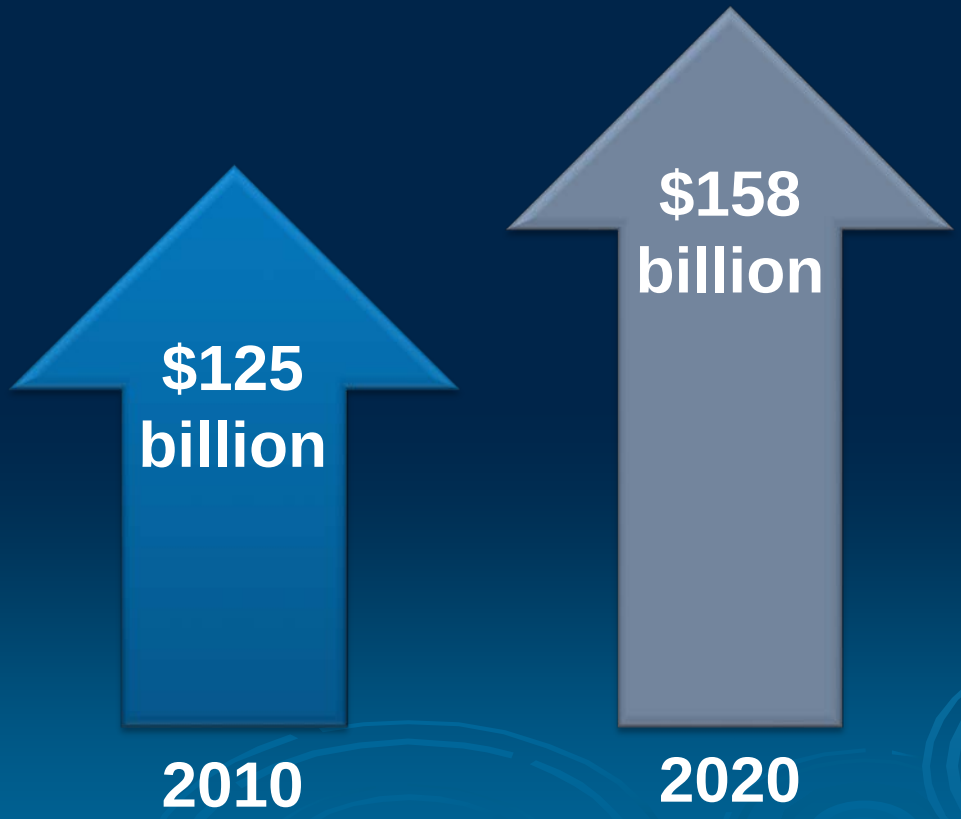
Misconceptions

- Oral chemotherapy is less toxic
- Patients prefer to take oral chemotherapy
- Oral chemotherapy regimens are simple to administer
- Oral chemotherapy is safer to handle

J Natl Compr Canc Netw 2008;6(3):S1-15.

Costs

- The cost of cancer care is the most rapidly increasing component of U.S. health care spending



Fed Pract 2016;33(1):22S-25S

Pharmacy Practice Standard for Oral Oncolytics

Pharmacy Practice Standard

- Developed by the Hematology/Oncology Pharmacy Association (HOPA) for pharmacist's involvement in oral oncolytic management

Prescribing

Education

Dispensing/ Distribution

Monitoring/ Follow-up

J Oncol Pract 2019;15:e346-55

Prescribing

- Responsible for safe, effective, and consistent prescribing
- Role in drug selection
- Order templates for prescribing
- Medication review at the time of prescription

J Oncol Pract 2019;15:e346-55

Education

- Diagnosis/indication
- Goals of treatment
- Duration and schedule of treatment
- Drug-drug and drug-food interactions
- Adverse effects
- Safe handling and disposal
- Follow up

J Oncol Pract 2019;15:e346-55

Dispensing / Distribution

J Oncol Pract 2019;15:e346-55

Monitoring: Symptom Management

- Wide variety of adverse effects
- Drug therapy for symptom management
- Ordering ability for relevant laboratory tests
- Follow up within the first 2 weeks of initiation
- Report to FDA MedWatch program

J Oncol Pract 2019;15:e346-55

Monitoring: Adherence

- Imperative to maximize effectiveness
- Varies from 50% to 100%
- Barriers to adherence include:

Low Health Literacy

Limited Patient Knowledge

Complex Instructions

Adverse Effects

High Cost

J Oncol Pract 2019;15:e346-55

Pharmacologic Class Review

Pharmacologic Classes of Chemotherapy

- Alkylating agents
- Anthracyclines
- Antimetabolites
- Antineoplastic antibiotics
- Immunomodulators
- Kinase inhibitors
- Platinum-based agents
- Proteasome inhibitors
- Retinoids
- Taxanes
- Topoisomerase inhibitors
- Vinca alkaloids

Kinase Inhibitors

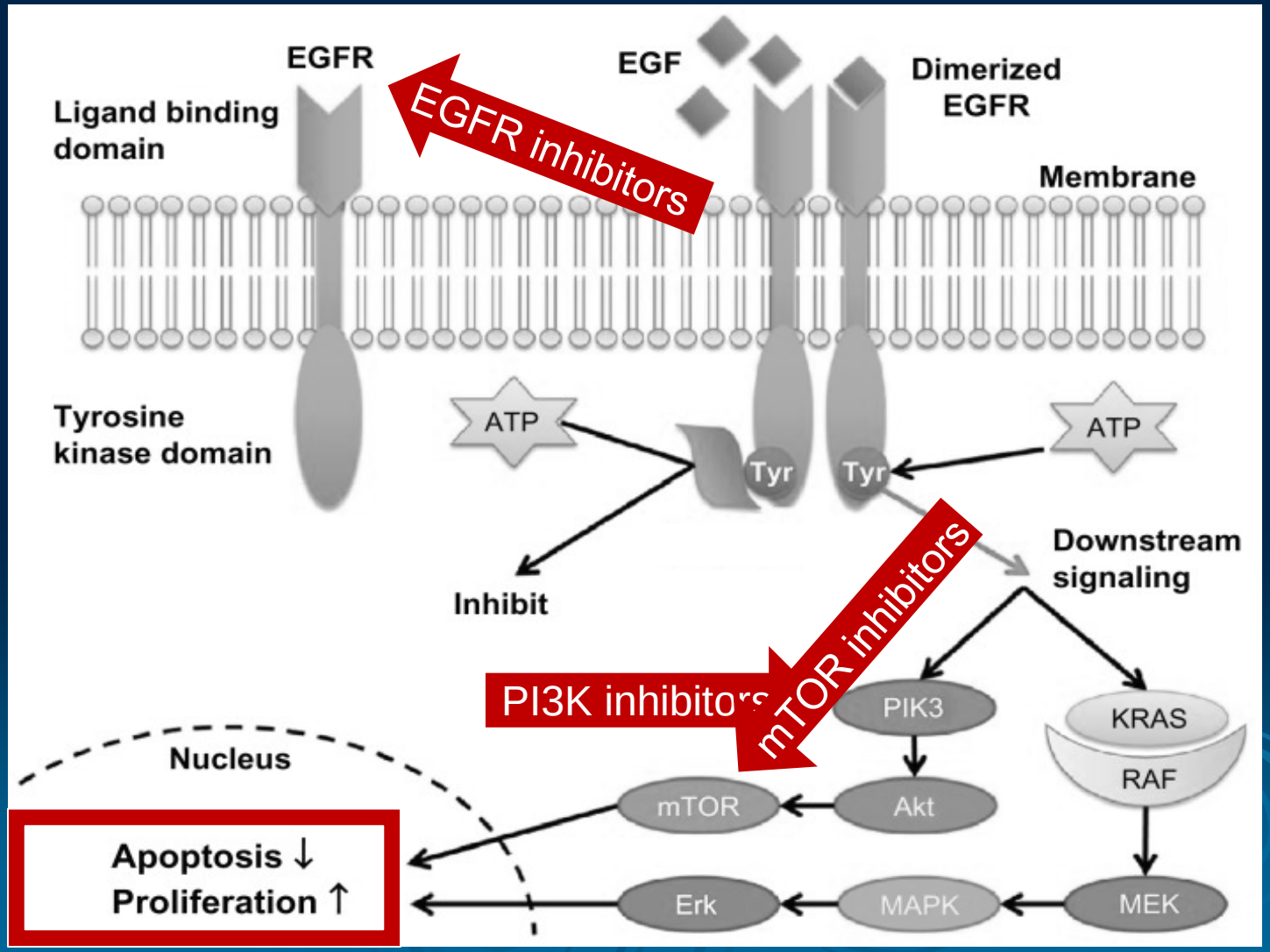
Tyrosine kinase inhibitors (TKIs)

- Anaplastic lymphoma kinase (ALK) inhibitors
- BCR-ABL tyrosine kinase inhibitors
- Bruton tyrosine kinase (BTK) inhibitors
- Epidermal growth factor receptor (EGFR) inhibitors
- Fibroblast growth factor receptor (FGFR) inhibitors
- FMS-like tyrosine kinase 3 (FLT3) inhibitors
- Janus kinase (JAK) inhibitors
- Mitogen-activated protein kinase (MEK) kinase inhibitors
- Tropomyosin receptor kinase (TRK) inhibitors
- Vascular endothelial growth factor receptor (VEGF) inhibitors

Serine/threonine kinase inhibitors

- BRAF kinase inhibitors
- Cyclin-dependent kinase (CKD) inhibitors
- Mammalian target of rapamycin (mTOR) kinase inhibitors
- Phosphatidylinositol 3-kinase (PI3K) inhibitors

Site of Action



Question 2

True or False

- Oral chemotherapy agents were developed within the last 20 years.

Recently Approved Oral Oncolytics

New Oncolytics: 2017

Generic Name (Brand Name)	Indication	Class	FDA Approval
Acalabrutinib (Calquence®)	Mantle cell lymphoma; chronic lymphocytic leukemia	BTK tyrosine kinase inhibitor	Oct 2017
Abemaciclib (Verzenio®)	Breast cancer	CDK inhibitor	Sept 2017
Enasidenib (Idhifa®)	Acute myeloid leukemia	IDH2 inhibitor	Aug 2017
Neratinib (Nerlynx®)	Breast cancer	EGFR tyrosine kinase inhibitor	July 2017
Brigatinib (Alunbrig®)	Non-small cell lung cancer	ALK tyrosine kinase inhibitor	Apr 2017
Midostaurin (Rydapt®)	Acute myeloid leukemia	FLT3 tyrosine kinase inhibitor	Apr 2017
Ribociclib (Kisqali®)	Breast cancer	CDK inhibitor	Mar 2017

Hematology/Oncology (Cancer) Approvals & Safety Notifications. FDA 2019

New Oncolytics: 2018

Generic Name (Brand Name)	Indication	Class	FDA Approval
Gilteritinib (Xospata®)	Acute myeloid leukemia	FLT3 tyrosine kinase inhibitor	Nov 2018
Larotrectini (Vitrakvi®)	Solid tumors	TRK inhibitor	Nov 2018
Glasdegib (Daurismo™)	Acute myeloid leukemia	Hedgehog pathway inhibitor	Nov 2018
Lorlatinib (Lorbrena®)	Non-small cell lung cancer	ALK tyrosine kinase inhibitor	Nov 2018
Talazoparib (Talzenna™)	Breast cancer	PARP inhibitor	Oct 2018
Dacomitinib (Vizimpro®)	Non-small cell lung cancer	EGFR tyrosine kinase inhibitor	Sept 2018
Duvelisib (Copiktra®)	Chronic lymphocytic leukemia; follicular lymphoma	PI3K inhibitor	Sept 2018
Encorafenib (Braftovi®)	Melanoma	BRAF kinase inhibitor	June 2018
Binimetinib (Mektovi®)	Melanoma	MEK inhibitor	June 2018

Hematology/Oncology (Cancer) Approvals & Safety Notifications. FDA 2019

New Oncolytics: 2019

Generic Name (Brand Name)	Indication	Class	FDA Approval
Zanubrutinib (Brukinsa™)	Mantle cell lymphoma	BTK tyrosine kinase inhibitor	Nov 2019
Fedratinib (Inrebic®)	Myelofibrosis	FLT3 tyrosine kinase inhibitor	Aug 2019
Entrectinib (Rozlytrek™)	Non-small cell lung cancer	TRK inhibitor	Aug 2019
Pexidartinib (Turalio™)	Tenosynovial giant cell tumor	CSF1R tyrosine kinase inhibitor	Aug 2019
Darolutamide (Nubeqa®)	Prostate cancer	Antiandrogen	July 2019
Selinexor (Xpovio™)	Multiple myeloma	Nuclear export inhibitor	July 2019
Alpelisib (Piqray®)	Breast cancer	PI3K inhibitor	May 2019
Erdafitinib (Balversa™)	Urothelial carcinoma	FGFR inhibitor	Apr 2019

Hematology/Oncology (Cancer) Approvals & Safety Notifications. FDA 2019

ALK Inhibitors

Alectinib (Alecensa®)

- Non-small cell lung cancer (NSCLC)

Brigatinib (Alunbrig®) NEW

- Non-small cell lung cancer (NSCLC)

Ceritinib (Zykadia®)

- Non-small cell lung cancer (NSCLC)

Crizotinib (Xalkori®)

- Non-small cell lung cancer (NSCLC)

Lorlatinib (Lorbrena®) NEW

- Non-small cell lung cancer (NSCLC)

Images courtesy of empr.com and thesocialmedwork.com

Brigatinib (Alunbrig®)

Indication

- ALK-positive advanced or metastatic NSCLC (second-line)

Dose

- 90 mg (1 tablet) PO daily x 7 days, then if tolerated increase to 180 mg (two 90 mg tablets) PO daily

Administration

- Take with or without food
- If treatment is interrupted for ≥ 14 days, resume treatment at 90 mg

Alunbrig (brigatinib) [package insert]

Brigatinib (Alunbrig®)

Warnings/Adverse Reactions

- Interstitial lung disease/pneumonitis 
- Hypertension
- Bradycardia
- Visual disturbances
- Hyperglycemia
- ↑ CPK levels and pancreatic enzymes

Drug Interactions

- CYP3A4 inducers (e.g. phenobarbital, phenytoin, rifampin, St. John's Wort)
- CYP3A4 inhibitors (e.g. ketoconazole, clarithromycin, diltiazem, verapamil)

Alunbrig (brigatinib) [package insert]

Lorlatinib (Lorbrena®)

Indication

- ALK-positive metastatic NSCLC (second or third-line)

Dose and Administration

- 100 mg (1 tablet) PO daily with or without food

Warnings/Adverse Reactions

- CNS effects (seizures, hallucinations, changes in mood, etc.)
- Hyperlipidemia
- Atrioventricular block
- Interstitial lung disease/pneumonitis

Drug Interactions

- Contraindicated with CYP3A4 inducers

Lorbrena (lorlatinib) [package insert]

BRAF Inhibitors

Dabrafenib (Tafinlar®)

- Melanoma
- Non-small cell lung cancer (NSCLC)
- Thyroid cancer

Encorafenib (Braftovi®)

NEW

- Colorectal cancer (off-label)
- Melanoma

Vemurafenib (Zelboraf®)

- Melanoma
- Non-small cell lung cancer (NSCLC) (off-label)

Image courtesy of empr.com

Encorafenib (Braftovi®)

Indication

- Unresectable or metastatic melanoma with a BRAF mutation in combination with binimetinib (Mektovi®)

Dose and Administration

- 450 mg (six 75 mg capsules) PO daily in combination with binimetinib

Warnings/Adverse Reactions

- Hemorrhage
- Uveitis
- QT prolongation

Drug Interactions

- CYP3A4 inhibitors and inducers

Braftovi (encorafenib) [package insert]

MEK Inhibitors

Binimetinib (Mektovi®)

NEW

- Colorectal cancer (off-label)
- Melanoma

Cobimetinib (Cotellic®)

- Melanoma

Trametinib (Mekinist®)

- Melanoma
- Non-small cell lung cancer (NSCLC)
- Thyroid cancer

Image courtesy of fiercebiotech.com

Binimetinib (Mektovi®)

Indication

- Unresectable or metastatic melanoma with a BRAF mutation in combination with encorafenib (Braftovi®)

Dose and Administration

- 15 mg (1 tablet) PO daily in combination with encorafenib

Warnings/Adverse Reactions

- Cardiomyopathy
- Venous thromboembolism
- Ocular toxicities (retinopathy, uveitis)
- Interstitial lung disease/pneumonitis 
- Hepatotoxicity
- Rhabdomyolysis
- Hemorrhage

Binimetinib (Mektovi) [package insert]

BTK Inhibitors

Zanubrutinib (Brukinsa™)

NEW

- Mantle cell lymphoma

Acalabrutinib (Calquence ®)

- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Mantle cell lymphoma

Ibrutinib (Imbruvica®)

- Chronic lymphocytic leukemia (CLL)
- Small lymphocytic lymphoma (SLL)
- Mantle cell lymphoma

Image courtesy of fiercepharma.com

Zanubrutinib (Brukinsa™)

Indication

- Mantle cell lymphoma (second-line)

Dose and Administration

- 160 mg (two 80 mg capsules) PO twice daily or 320 mg (four 80 mg capsules) PO daily
- Swallow capsules whole with full glass of water

Warnings/Adverse Reactions

- Hemorrhage
- Infections
- Cytopenias
- Arrhythmias

Drug Interactions

- CYP3A4 inducers and inhibitors

Brukinsa (zanubrutinib) [package insert]

CDK Inhibitors

Abemaciclib (Verzenio®)

NEW

- Breast cancer

Palbociclib (Ibrance®)

- Breast cancer

Ribociclib (Kisqali®)

NEW

- Breast cancer

Images courtesy of en.50bestpharma.com and clinicaltrialsarena.com

Abemaciclib (Verzenio®)

Indication

- HR+, HER2- advanced or metastatic breast cancer

Dose and Administration

- In combination: 150 mg (1 tablet) PO twice daily
- As monotherapy: 200 mg (1 tablet) PO twice daily

Warnings/Adverse Reactions

- Diarrhea
- Neutropenia
- Interstitial lung disease/pneumonitis 
- Hepatotoxicity
- Venous thromboembolism

Drug Interactions

- CYP3A4 inhibitors and inducers

Verzenio (abemaciclib) [package insert]

Ribociclib (Kisqali®)

Indication

- HR+, HER2- advanced or metastatic breast cancer

Dose and Administration

- 28-day cycle: 600 mg (three 200 mg tablets) PO daily x 21 days, followed by 7 days off

Warnings/Adverse Reactions

- Interstitial lung disease/pneumonitis 
- QT prolongation
- Neutropenia

Drug Interactions

- CYP3A4 inhibitors and inducers
- Tamoxifen

Kisqali (ribociclib) [package insert]

FLT3 Inhibitors

NEW

Fedratinib (Inrebic®)

- Myelofibrosis

NEW

Gilteritinib (Xospata®)

- Acute myeloid leukemia (AML)

NEW

Midostaurin (Rydapt®)

- Acute myeloid leukemia (AML)
- Mast cell leukemia

Images courtesy of clinicaltrialsarena.com and hcp.novartis.com

Gilteritinib (Xospata®)

Indication

- Relapsed or refractory AML with a FLT3 mutation

Dose and Administration

- 120 mg (3 tablets) PO daily for a minimum of 6 months

Warnings/Adverse Reactions

- Posterior reversible encephalopathy syndrome (PRES)
- QT prolongation
- Pancreatitis

Black Box Warning

- Differentiation syndrome

Xospata (gilteritinib) package insert]

Midostaurin (Rydapt®)

Indication

- Newly diagnosed AML with a positive FLT3 mutation in combination with standard 7+3 induction therapy

Dose and Administration

- 50 mg (two 25 mg capsules) PO twice daily with food

Warnings/Adverse Reactions

- Interstitial lung disease/pneumonitis
- Neutropenia
- Mucositis

Drug Interactions

- CYP3A4 inducers and inhibitors

Rydapt (midostaurin) package insert]

FGFR Inhibitor

Erdafitinib (Balversa®)

NEW

- Urothelial carcinoma

Image courtesy of empr.com

Erdafitinib (Balversa®)

Indication

- Locally advanced or metastatic urothelial carcinoma with FGFR mutation (second-line)

Dose and Administration

- 8 mg PO daily; increase to 9 mg after 14-21 days if tolerated

Warnings/Adverse Reactions

- Ocular disorders
- Hyperphosphatemia

Drug Interactions

- CYP2C9 inducers and inhibitors
- CYP3A4 inducers and inhibitors

Balversa (erdafitinib) package insert]

IDH2 Inhibitor

Enasidenib (Idhifa®)

NEW

- Acute myeloid leukemia (AML)

Image courtesy of cancerhealth.com

Enasidenib (Idhifa®)

Indication

- Relapsed or refractory AML with an IDH2 mutation

Dose and Administration

- 100 mg (1 tablet) PO daily with a full glass of water
- Moderate emetic potential

Adverse Reactions

- Nausea/vomiting
- Diarrhea
- Decreased appetite

Black Box Warning ⚠

- Differentiation syndrome

Idhifa (enasidenib) [package insert]

PI3K Inhibitors

Idelalisib (Zydeliq®)

- Chronic lymphocytic leukemia (CLL)
- Follicular lymphoma (FL)

Duvelisib (Copiktra®)

NEW

- Chronic lymphocytic leukemia (CLL)
- Follicular lymphoma (FL)

Alpelisib (Piqray®)

NEW

- Breast cancer

Image courtesy of hcp.novartis.com and empr.com

Alpelisib (Piqray®)

Indication

- HR+, HER2-, PIK3CA-mutated advanced or metastatic breast cancer in postmenopausal women taking concomitant fulvestrant

Dose and Administration

- 300 mg (two 150 mg tablets) PO daily with food
- Doses missed by > 9 hours should be skipped

Warnings/Adverse Reactions

- Severe cutaneous reactions
- Hyperglycemia
- Pneumonitis
- Severe diarrhea

Drug Interactions

- Warfarin
- CYP3A4 inducers

Piqray (alpelisib) [package insert]; Image courtesy of healthcentral.com

Duvelisib (Copiktra®)

Indication

- Relapsed or refractory CLL/SLL
- Follicular lymphoma (third-line)

Dose and Administration

- 25 mg (1 capsule) PO twice daily
- Doses missed by > 6 hours should be skipped
- PCP prophylaxis

Warnings/Adverse Reactions

- Neutropenia
- Hepatotoxicity

Black Box Warnings

- Infections
- Diarrhea or colitis
- Cutaneous reactions
- Pneumonitis

Copiktra (duvelisib) [package insert]

TRK Inhibitors

NEW

Entrectinib (Rozlytrek®)

- Non-small cell lung cancer (NSCLC)
- Solid tumors

NEW

Larotrectinib (Vitrakvi®)

- Solid tumors

Images courtesy of empr.com

Entrectinib (Rozlytrek®)

Indication

- NSCLC with ROS1-positive tumors
- Adult or pediatric solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion

Dose and Administration

- NSCLC: 600 mg (three 200 mg capsules) PO daily
- Adult solid tumors: 600 mg (three 200 mg capsules) PO daily

Warnings/Adverse Reactions

- Congestive heart failure
- CNS effects
- Hepatotoxicity
- Hyperuricemia
- QT prolongation
- Vision disorders

Rozlytrek (entrectinib) [package insert]

Larotrectinib (Vitrakvi®)

Indication

- Adult or pediatric solid tumors with a neurotrophic receptor tyrosine kinase (NTRK) gene fusion

Dose and Administration

- Adults: 100 mg (1 capsule) PO twice daily
- Pediatrics: 100 mg/m^2 PO twice daily

Warnings/Adverse Reactions

- Neurotoxicity
- Hepatotoxicity

Drug Interactions

- CYP3A4 inducers and inhibitors

Vitrakvi (larotrectinib) [package insert]

Question 3

True or False

- Alpelisib (Piqray®) should not be used in patients with Type 1 diabetes or uncontrolled Type 2 diabetes.

Key Points

ALK inhibitors
CDK Inhibitors
PI3K Inhibitors
Alpelisib (Piqray®)
Binimetinib (Mektovi®)
Midostaurin (Rydapt®)

AVOID:

Encorafenib (Braftovi®)
Entrectinib (Rozlytrek®)
Gilteritinib (Xospata®)
Ribociclib (Kisqali®)

Key Points

CAUTION:
Brigatinib (Alunbrig®)
Alpelisib (Piqray®)

Erdafitinib (Balversa®)
Entrectinib (Rozlytrek®)

Alpelisib (Piqray®)
Midostaurin (Rydapt®)

Resources

Oral Chemotherapy Chart

- https://info.avella.com/oral-chemo-chart

OncoLink

- https://www.oncolink.org/

National Comprehensive Cancer Network (NCCN)

- https://www.nccn.org/

Thank You

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References

1. NCI Dictionary of Cancer Terms. National Cancer Institute. https://www.cancer.gov/publications/dictionaries/cancer-terms. Published 2019. Accessed December 31, 2019.
2. Weingart SN, Brown E, Bach PB, et al: NCCN task force report: Oral chemotherapy. *J Natl Compr Canc Netw* 2008;6(3):S1-15.
3. Dahl BJ. The cost of oncology drugs: A pharmacy perspective, part I. *Fed Pract* 2016;33(1):22S-25S.
4. Mackler E, Segal EM, Muluneh B, et al. 2018 Hematology/oncology pharmacist association best practices for the management of oral oncolytic therapy: Pharmacy practice standard. *J Oncol Pract* 2019;15:e346-55.
5. Kinase Inhibitors for Cancer Treatment. Chemoth.com. https://chemoth.com/types/kinaseinhibitors. Published 2020. Accessed January 5, 2020.
6. Hematology/Oncology (Cancer) Approvals & Safety Notifications. U.S. Food and Drug Administration. https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications. Published 2019. Accessed December 30, 2019.
7. Alunbrig (brigatinib) [package insert]. Cambridge, MA:ARIAD Pharmaceuticals, Inc.;2017.
8. Lorbrena (lorlatinib) [package insert]. New York, NY: Pfizer Inc,;2018.
9. Braftovi (encorafenib) [package insert]. Boulder, CO: Array BioPharma Inc.;2018.
10. Binimetinib (Mektovi) [package insert]. Boulder, CO: Array BioPharma Inc.;2018.

References

11. Brukinsa (zanubrutinib) [package insert]. San Mateo, CA: BeiGene, Ltd.;2019.
12. Verzenio (abemaciclib) [package insert]. Indianapolis, IN: Lilly USA, LLC;2017.
13. Kisqali (ribociclib) [package insert]. East Hanover, NJ: Novartis;2017.
14. Xospata (gilteritinib) package insert]. Northbrook, IL: Astellas Pharma US, Inc.;2018.
15. Rydapt (midostaurin) package insert]. East Hanover, NJ: Novartis;2017.
16. Balversa (erdafitinib) package insert]. Horsham, PA: Janssen Products, LP;2019.
17. Idhifa (enasidenib) [package insert]. Cambridge, MA: Agios Pharmaceuticals;2019.
18. Piqray (alpelisib) [package insert]. East Hanover, NJ: Novartis;2019.
19. Copiktra (duvelisib) [package insert]. Needham, MA: Verastem, Inc.;2018.
20. Rozlytrek (entrectinib) [package insert]. South San Francisco, CA: Genentech USA, Inc.;2019.
21. Vitrakvi (larotrectinib) [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.;2018.